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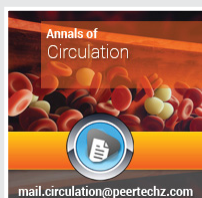
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# Annals of Circulation

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Jules C Hancox<sup>1\*</sup> and A Graham Stuart<sup>2</sup>

<sup>1</sup>School of Physiology, Pharmacology and Neuroscience, University of Bristol, United Kingdom

<sup>2</sup>Bristol Heart Institute, University of Bristol, United Kingdom

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\*Corresponding author: Jules C Hancox, Professor, School of Physiology, Pharmacology and Neuroscience, Biomedical Sciences Building, University Walk, Bristol, BS8 1TD, United Kingdom. Tel: +44-117-3312292; Email: [jules.hancox@bristol.ac.uk](mailto:jules.hancox@bristol.ac.uk)

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## Opinion

# Rational prediction of pharmacological treatment options for a novel KCNH2-linked variant of the Short QT Syndrome

## Opinion

Congenital disorders of cardiac repolarization are associated with risk of serious arrhythmias and sudden death. The Long QT Syndrome (LQTS) is well-established to predispose towards torsades de pointes [1]. The Short QT Syndrome (SQTs) is a more recently discovered condition involving abbreviated repolarization that predisposes to atrial and ventricular arrhythmias and sudden death [2]. It is characterized by short QT intervals on the electrocardiogram, frequently with tall upright T waves and by a poor rate adaptation of the QT interval: short QT intervals persist even at slow heart rates [2-4]. Due to the risk of sudden death, SQTs patients are often treated with implantable cardioverter defibrillators (ICDs). Mutations to genes that encode critical components of cardiac potassium channels have been implicated in the syndrome: *KCNH2* in SQT1, *KCNQ1* in SQT2 and *KCNJ2* in SQT3 [2-4]. Of successfully genotyped cases, the most prevalent mutations affect *KCNH2* [3]. *KCNH2* (alternative nomenclature *hERG*: *human-Ether-à-go-go-Related Gene*) is responsible for encoding the pore-forming protein of channels that mediate the cardiac rapid delayed rectifier current,  $I_{Kr}$  [5].  $I_{Kr}$  is vital for normal ventricular repolarization, evidenced by the fact that loss-of-function mutations in *hERG*-mediated subunits underpin the LQT2 form of congenital Long QT Syndrome [1,5]. Gain-of-function mutations in *hERG*-mediated subunits underpin variant 1 (SQT1) of the SQTs [2,3].

The gene mutations with the largest effects on *hERG*/ $I_{Kr}$  channel current amplitude and kinetics in the SQTs give rise to an asparagine to lysine (N→K) substitution (N588K) in the external S5-Pore linker region that contributes to

control of the process of *hERG* channel inactivation [6-9]. The N588K mutation results in a profound positive voltage-shift in the inactivation of the *hERG*/ $I_{Kr}$  channel; this in turn results in greater repolarizing current, timed earlier during ventricular action potentials [6,8,9], resulting in accelerated repolarization and an SQTs phenotype. *hERG* is a target of Class III antiarrhythmic drugs, including methanesulphonanilides such as sotalol and dofetilide and the N588K mutation was found significantly to impair the ability of this class of drugs to interact with the *hERG* channel [6,10-12].

Very recently a new SQT1 mutation has been reported involving a serine to alanine (S→A) substitution (S631A) in the *hERG* channel pore region [13]. The index patient was screened at the age of 6 following the sudden death of a cousin and was found to have a rate-corrected (QTc) QT interval below 320 ms. She was without symptoms until experiencing syncope ten years later during physical exertion and then underwent ICD implantation [13]. Her father was asymptomatic but also possessed a shortened QTc interval (324 ms). Her sister also possessed a shortened QTc interval (340 ms) and a modest reduction in left ventricular ejection fraction (to 47%), but without other cardiac symptoms. Neither she nor the father underwent ICD implantation [13]. An asymptomatic brother did not possess a short QT interval. However, the father had a sister who had died suddenly at 30 and another sister with two sons who had died suddenly [13]. On genetic screening, the proband, her sister and father were found to have the S631A mutation, whilst her asymptomatic brother did not [13]. The index patient also possessed an *SCN10A* variant (R1869C), but her father did not and her mother, who did not have a short QT interval, did have the *SCN10A* variant [13]. This suggests that the *hERG* mutation and not the *SCN10A* variant was responsible for the SQTs phenotype in this family [13].

The identification of the S631A *hERG* mutation in clinical SQTs is interesting in a number of respects. Although this recent report is the first to implicate the mutation in clinical SQTs, the S631A mutation has long been used in basic science investigations to study the *hERG*/ $I_{Kr}$  channel's P-type inactivation process [14,15]. It produces a profound

(>100 mV) positive shift in voltage-dependent inactivation of hERG current, without affecting voltage dependent activation [15]. Under action potential voltage clamp, S631A produced changes to hERG current profile during the ventricular action potential [16], that are very similar to those reported much later for N588K [6,8,9]. It is highly likely, therefore, that mechanisms of proarrhythmia are also similar to those reported for N588K using computational modelling [17]. Perhaps most significantly, there already exists a sizeable body of pharmacological literature on the S631A hERG mutation. For example, a study from 2000 identified that the sensitivity of hERG to the class III antiarrhythmic drug dofetilide was greatly attenuated by the S631A mutation, whilst that to the class Ia drug quinidine was little altered [18]. Work from this laboratory subsequently identified that a second class Ia drug, disopyramide, was able to block S631A hERG channels [19], and in a subsequent side-by-side comparison of S631A and N588K, we found similarly modest attenuating effects of the two individual mutations on the potencies of disopyramide and quinidine, whilst combining the 2 mutations (which produces a greater attenuation of inactivation) had a greater effect on the actions of the two drugs [12]. Unlike sotalolol, quinidine is effective in the treatment of N588K-linked SQT1 [2,3,6,10], and disopyramide has some effectiveness too [20]. Given the preclinical pharmacological data on S631A hERG channels, it is reasonable cautiously to propose that both quinidine and disopyramide may have potential value in cases of S631A hERG mutation linked SQT1, delaying repolarization and prolonging refractoriness in this setting. In principle, these drugs could be of prophylactic use in patients with this mutation in whom ICDs were not fitted, or as an adjunct therapy in patients with such devices.

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